REMARKS/ARGUMENTS

Independent claims 1, 35, and 75 have been amended to recite the specific particle size distribution of the Dey FP formulation found to provide surprising results as discussed in the Examples section of one of the parent applications (i.e., U.S. Publication No. 2004/0208830 (Ser. No. 10/414,682)). Applicant notes that the Dey FP formulation used in the Examples section of Ser. No. 10/414,682 had the same particle size distribution recited in each of the currently amended claims and contained 0.05% by weight of fluticasone. As provided in paragraph [0001] of the published application (i.e., U.S. Publication No. 2004/0209852), Publication No. 2004/0208830 (Ser. No. 10/414,682) has been incorporated by reference in its entirety. Further, the present application is a continuation-in-part of Ser. No. 10/414,682. Support for the recited particle size distribution can be found at least on Table 1 in the Examples section of Publication No. 2004/0208830 (Ser. No. 10/414,682). Dependent claim 10 has been amended to recite about 50 mcg of the steroidal anti-inflammatory. Claims 14-15 have been cancelled. No new matter has been entered.

I. The Currently Claimed Invention

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of rhinitis comprising an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone having a specific suspended solid particle size distribution profile (shown to provide surprising results) characterized by 5 different micron ratings of the solid fluticasone particles in combination with an antifungal agent. The fluticasone particle size distribution claimed has surprisingly shown to provide increased bioavailability over conventional formulations as evident by the factually reported increased magnitude of improvement in several patients (e.g., reduction in the signs and symptoms of seasonal allergic rhinitis (SAR)). That is, patients receiving the currently claimed formulations which recite the particular particle size distribution (i.e., a particular distribution for fluticasone shown to provide surprising results) attributed to the increased magnitude of improvement realize a surprisingly increased reduction in the symptoms of SAR. As discussed in further detail below, the currently

claimed formulations were compared to Flonase. The recited particle size distribution for fluticasone was the only difference from the Flonase formulation.

II. Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit ''no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.'' *Id.* at ___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that '' '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' '' *Id.* at ___, 82 USPQ2d at 1396.

A.

Claims 1, 4-6, 10-15, 22-25, 27-30, and 35 stand rejected under 35 U.S.C. §103(a) as being obvious over "FLONASE®" from the online Physician's Desk Reference ("PDR®), as

evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Lacy") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini"), WO 99/18971 to Harris (hereinafter "Harris"), and U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken"). The Office has indicated that Harris is provided merely as a supporting reference to demonstrate particle sizes recognized in the art.

Applicant submits that each of Flonase, Bernini, Osbakken, and Harris fail to teach, suggest, or render predictable each and every element as recited in independent claims 1, 35, and 75 or any claims dependent thereon. Specifically, none of the cited references teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75.

Flonase is a 50 mcg of microcrystalline aqueous suspension of fluticasone propioinate. Flonase can be used for the perennial rhinitis in patients above 12 years of age. See Lacy. As discussed in paragraphs [0053] – [0090] of Publication No. 2004/0208830 (Ser. No. 10/414,682), which was incorporated by reference in its entirety, a controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than Flonase (i.e., the Dey FP nasal spray had a different particle size distribution then Flonase). The Office acknowledges that Lacy does not teach the currently claimed particle size distributions, but that the particle size distribution is obviated by the teachings of Bernini.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs. Bernini's process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients (i.e.

fluticasone dipropionate); and (iv) dispersing all of the ingredients by using the sameturboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the fluticasone is deposited into the lungs.

However, each of Flonase, Bernini, and Harris fail to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. As discussed below, Osbakken fails to cure these deficiencies.

The Office relies on Osbakken for the teaching of formulations including an antifungal agent or an antibiotic.

Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092]. As noted in previous responses, Osbakken is directed to solutions of dissolved active as opposed to suspensions of solid active.

Thus, despite teaching solutions containing both an anti-inflammatory and an antifungal agent, Osbakken fails to cure all of the deficiencies noted in Flonase, Bernini, Hasrris, and any combination thereof. As such, any combination the Osbakken, Flonase, Bernini, and Harris also fails to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited

in independent claims 1, 35, and 75. As such, each of the cited references, alone or in any combination, fails to teach, suggest or render predictable every element currently recited in independent claims 1, 35, and 75 (or any claims dependent thereon). As such, Applicant submits that this obviousness rejection has been overcome. Applicants request withdrawal of this rejection.

B.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade").

The Office relies on Doi for teaching suspensions for nasal applications containing citric acid and EDTA. The Office cites Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the

endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, neither Doi, Meade, nor any combination thereof cure the aforementioned deficiencies of Flonase, Bernini, Osbakken, or any combination thereof. As such, any combination the Osbakken, Flonase, and Bernini also fails to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. Therefore, Doi, Meade, or any combination thereof fail to cure the deficiencies of the Flonase/Bernini or Flonase/Bernini/Osbakken. Applicant requests withdrawal of this rejection.

C.

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of "Management of Allergic Rhinitis", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy").

The Office relies on Walker and Hamuy to show that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are will-known anti-viral agents (Hamuy).

Applicant notes, however, that none of Walker, Hamuy, or the combination of the two cures the deficiencies noted above. In particular, neither of these secondary references teach, suggest or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended

solid fluticasone particles; (2) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. Thus, Applicant requests withdrawal of this rejection.

D. Surprising Results

At the outset, the Office appears to cite paragraph [0086] of serial number 10/414,682, which has been incorporated into the present application by reference, for stating that there was no statistically significant difference between Dey-FP and Flonase High and Low Dose groups. However, the Office is ignoring the rest of the sentence which provides that the treatment groups behaved similarly, "except for the magnitude of improvement in TNSS." As such, Applicant disagrees with the Office's characterization of the results in each study.

1. Clarification of the weight percent of fluticasone in the Dey FP formulation used in the study described in Ser. No. 10/414,682

On page 16 of the present Office action, the Office states that it is unclear whether the Dey FP 50 mcg formulation used in the study correlates to the recited range for the weight percent of fluticasone. Applicant submits that the individual contents of the Dey FP formulation along with their respective weight are provided in Table 3 of Ser. No. 10/414,682. Table 3 has been provided below for ease of reference.

TABLE 3

Formulation of Fluticasone Propionate Nasal Spray

INGREDIENT	FUNCTION	DRUG PRODUCT CONCENTRATION	PER SPRAY	PER BOTTLE
Fluticasone Propionate USP	Active Ingredient	0.050% w/w	0.050 mg	8.00 mg
Benzalkonium Choloride Solution 50% NF	Preservative	0.020% w/w	0.0388 mg	6.21 mg
Microcrystalline Cellulose/Carboxymethy-cellose Sodium NF	Suspension Agent	1.50% w/w	1.50 mg	240.0 mg
Polysorbate 80 NF	Wetting Agent	0.005% w/w	0.005 mg	0.80 mg
Phenylethyl Alcohol USP	Preservative	0.25% v/w	0.255 mg	40.80 mg
Dextrose, Anhydrous USP	To adjust osmolality	5.00% w/w	5.00 mg	800.0 mg
Hydrochloric Acid 1N	To adjust pH	As required	As required	As required
Purified Water USP	Diluent	n/a	93.15 mg	14.90 g

As can be seen from Table 3 above, the "per spray" amount of fluticasone is 0.05 mg while the total "per spray" mass is 100mg. Thus, the weight percent of fluticasone is (0.05mg /100mg)*100 = 0.05%. Applicant notes that the same weight percent can be computed from the "per bottle" values as well. That is, (8 mg / 15,996mg) *100 = 0.05%.

2. Clarification of "high dose" / "low dose" terminology in the fluticasone study

On pages 10 and 16 of the present Office Action, the Office states that it is unclear what constitutes a "high dose" and a "low dose". Stated differently, the Office has requested clarification as to the dosage amounts for what is referred to as a "high dose" and a "low dose". As explained below, the "high dose" / "low dose" designations refer to the number of sprays including fluticasone received by patients. "Low dose" groups only received 1 spray of fluticasone per nostril in a day while "high dose" groups received 2 sprays of fluticasone per nostril over the course of a day. Thus, patients in the "low dose" groups received half the amount of fluticasone than those in the "high dose" groups.

At the outset, Applicant notes that both the Dey FP and the Flonase formulations included 50 mcg of fluticasone. However, the fluticasone used in the Dey FP nasal spray was derived from a different source from that Flonase. That is, the particle size distribution of fluticasone in the Dey FP formulation was different than that of the Flonase formulation. Other than this difference, both the Dey FP and Flonase nasal sprays contained the same excipients and additives in the same amounts. Furthermore, the Dey FP nasal spray and the Flonase spray were each administered by the same metered-dose, manual pump spray.

Accordingly, the study used a single Dey FP formulation (having the recited particle size distribution) and a single Flonase formulation. Both the Dey FP formulation and the Flonase formulation contained 50 mcg of fluticasone. Patients were randomly assigned to one of six treatment groups. The first group was designated as the Dey FP Low Dose group. Patients in this group received 1 spray of Dey FP in each nostril 1 time during the day. The second group was designated as the Dey FP High Dose group. Patients in this group received 1 spray of Dey FP in each nostril 2 times per day. Thus, patients in the second group (i.e., Dey FP High Dose group) received twice as much fluticasone, namely 200 mcg total, as patients in the first group (i.e., Dey FP Low Dose group), which received 100 mcg total. The third group of patients was designated as the Flonase Low Dose group. Patients in this group received 1 spray of Flonase in each nostril 1 time during the day. The fourth group of patients was designated as the Flonase High Dose group. Patients in this group received 1 spray of Flonase in each nostril 2 times daily. Thus, the patients in the Flonase High Dose group received twice as much fluticasone than patients in the Flonase Low Dose and Dey FP groups (i.e., the Flonase High Dose group received a daily total of 200 mcg and the Flonase Low Dose group received 100 mcg). The fifth group of patients was designated as one of the placebo groups. Patients in this group received 1 spray of placebo in each nostril daily. The sixth group was also a placebo group, but they received 1 spray of placebo in each nostril 2 times daily.

Thus, patients in the High Dose groups (i.e., Dey FP High Dose and Flonase High Dose) received twice the amount of fluticasone than patients in the Low Dose groups (i.e., Dey FP Low Dose and Flonase Low Dose). That is, patients in each of the "low dose" groups received only 1 sprays of fluticasone in each nostril over the course of a day, while

patients in the "high dose" groups received 2 sprays of fluticasone in each nostril over the course of a day. As such, patients in the "low dose" groups received a total of 100 mcg of fluticasone over the course of a day while the patients in the "high dose" groups received 200 mcg of fluticasone over the course of the day.

3. Improvement in magnitude of TNSS reduction realized by patients in the Dey FP Low Dose group

The patients in the Dey FP Low Dose groups realized a superior relief of the symptoms of SAR over patients in the Flonase Low Dose group. Figure 1 of 10/414,682 provides a visual illustration of this increased relief from the symptoms of SAR. Table 1, provided below, provides an approximate quantitative value for the improved relief from the symptoms of SAR realized by patients in the Dey FP Low Dose group.

Table 1

Day	Dey FP Low Dose Group – approximate LS value	Flonase Low Dose Group – approximate LS value	% Improvement in TNSS over the Flonase Low Dose Group
7	-5.9	-4.5	**~31%**
8	-5.8	-5.1	**~14%**
9	-6.3	-5.8	**~9%**
10	-6.8	-6.2	**~10%**
11	-7.4	-5.6	**~21%**
12	-7.4	-6.1	**~19%**
13	-7.4	-6.2	**~19%**
14	-7.8	-6.5	**~20%**

Applicant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize the aforementioned percentages of TNSS improvement as not merely a minor difference of degree as suggested by the Office. Applicant notes that the patients in the Dey FP Low Dose group realized these improved reductions in TNSS while receiving the same amount of fluticasone than the patients in the Flonase Low Dose

group. Again, the only difference in the Dey FP and Flonase formulations is the respective particle size distributions.

4. Patients in the Dey FP Low Dose group realized improved or at least similar reduction in TNSS than both High Dose groups

After about 7 days, as illustrated by Figure 1, the patients of the Dey FP Low Dose group consistently reported a reduction in TNSS better than or substantially equal to that of patients in the Flonase High Dose group. Applicant first submits that the data from the Dey FP Low Dose group shows an improvement over results realized by patients in the Flonase High Dose group. Irrespective of Applicants stance that the data or the Dey FP Low Dose group shows improvement of the Flonase High Dose group, Applicant notes that the Office's view that the data sets for the Dey FP Low Dose and the Flonase High Dose groups are essentially the same also illustrates the surprising results realized by the currently claimed formulations (having the specifically recited particle size distribution). For instance, the patients of the Dey FP Low Dose group received half the fluticasone than the Flonase High Dose group. In view of the Office's characterization of the data sets, therefore, the Dey FP Low Dose group realized the same relief from the symptoms of SAR as the Flonase High Dose group despite receiving half the amount of fluticasone. The ability to achieve the same or similar relief from the symptoms of SAR while using half the amount of fluticasone is surprising in and of itself. That is, these results were unexpected because the skilled artisan would not have expected the Dey FP Low Dose group to realize improved relief in TNSS greater than or the same as the Flonase High Dose group (which received double the medicament).

The fact that the claimed distributions afford unexpected results provides further evidence of the non-obviousness of the currently claimed invention.

III. Double Patenting

Claim 1 stands provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending U.S. Application No. 11/931,484 in view of Lacy and Hebrecht, R. et al. "Voriconazole versus amphotericin B for

primary therapy of invasive aspergillosis" N. Eng. J. Med., 2002, 347(6), pp 408-415 (hereinafter "Hebrecht"). Applicants traverse this provisional rejection.

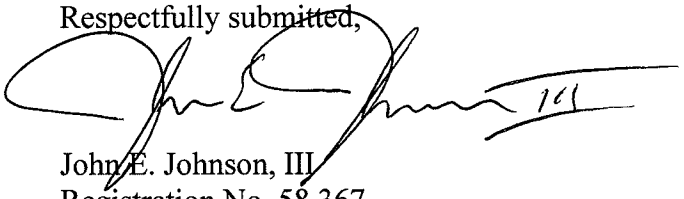
Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

IV. Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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